

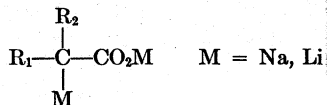
**$\alpha$  Anions of Carboxylic Acids. I.  
Effect of Hexamethylphosphoramide on  
Metalation and Alkylation**

PHILIP E. PFEFFER AND LEONARD S. SILBERT

*Eastern Utilization Research and Development Division,<sup>1</sup>  
Philadelphia, Pennsylvania 19118*

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$\alpha$  anions of carboxylic acids (I) offer unique oppor-



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tunities in synthesis. Unfortunately, their utility has not been investigated with acids other than acetic acid<sup>2</sup> and methyl-branched acids of chain lengths no greater than C<sub>4</sub>.<sup>3</sup> Typically, disodio derivatives con-

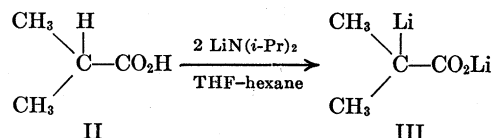
(1) Agricultural Research Service, U. S. Department of Agriculture.

(2) D. O. DePree and R. D. Closson, *J. Amer. Chem. Soc.*, **80**, 2311 (1958).

(3) P. L. Creger, *ibid.*, **89**, 2500 (1967), and references cited therein.

taining saturated  $\beta$ -carbon atoms were found to be unstable at the temperatures necessary for their formation.<sup>2</sup>

Creger<sup>3</sup> has recently prepared lithium  $\alpha$ -lithio isobutyrate (III) in high yield by treating isobutyric acid (II) with 2 equiv of lithium diisopropylamide in tetra-



hydrofuran (THF)-hexane solution. Alkylation of this dianion in homogeneous solution with butyl bromide (iodide) gave 80% (89%) yield of 2,2-dimethylhexanoic acid.

We have made an effort to apply this procedure to the alkylation of straight-chain aliphatic acids and have found it to be quite unsatisfactory. In general, we observed that the reaction mixtures of straight-chain acid dianions are cloudy and heterogeneous, and furthermore, yields of the corresponding  $\alpha$ -butyl derivatives of  $n$ -aliphatic acids ( $\text{C}_7$ - $\text{C}_{18}$ ) are in the low range (29-44%) (Table I). Therefore, in order to effect the alkylation of long straight-chain acids, a modification was essential.

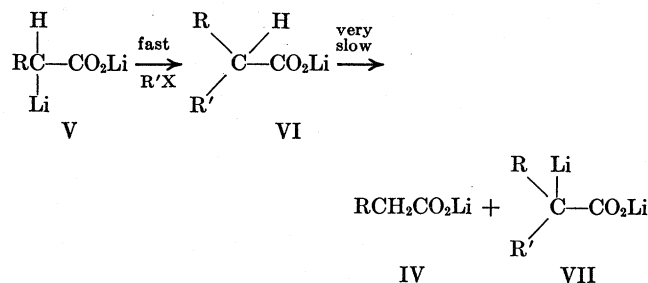
TABLE I  
PRODUCT YIELDS FROM REACTIONS OF STRAIGHT-  
AND BRANCHED-CHAIN METALATED  
ACIDS WITH BUTYL BROMIDE

Starting acid	% yield <sup>a</sup>	
	THF-hexane	THF-hexane-HMPA
Straight chain	2-Butyl Acid	
Heptanoic	43	93
Pelargonic	34	90
Myristic	29	90
Stearic	44 <sup>b</sup>	87 <sup>b,c</sup>
Branched chain	2,2-Dibutyl Acid	
Isobutyric	80	75
2-Butylheptanoic	50 <sup>d</sup>	15 <sup>e</sup>
2-Butylpelargonic	45	9

<sup>a</sup> All yields are based on distilled, recrystallized, or chromatographed product whose purity was determined by gas chromatographic analysis. Satisfactory elemental analyses and consistent ir, nmr, and mass spectra data were obtained for all products and are in accord with their reported values. <sup>b</sup> Best yields were obtained after stirring the dianion solution at room temperature for 1.5 hr. <sup>c</sup> Two equivalents of HMPA used. Some cloudiness was noted in the reaction mixture. <sup>d</sup> Product consisted of 30% 1-octene when the dianion of 2-butylheptanoic acid was treated with 1-bromooctane. <sup>e</sup> Product consisted of 80-85% 1-octene when the dianion of 2-butylheptanoic acid was treated with 1-bromooctane.

The use of hexamethylphosphoramide (HMPA) as cosolvent permitted the preparation of dianions in clear homogeneous solutions. The metalated  $n$ -aliphatic acids are then alkylated with  $n$ -butyl bromide to give  $\alpha$ -butyl acids in yields generally exceeding 90%. Examples of the reaction are recorded in Table I with the corresponding results of the unmodified method. Dialkylated acids were not observed even in trace amounts. One may conclude from this observation that lithium-hydrogen exchange between the straight-chain acid V and the  $\alpha$ -branched acid VI to generate the dianion of dialkyl acetic acid (VII) is not competitive with the very rapid nucleophilic attack of V on

R'X. This is equally the case for reactions in the absence of HMPA.



The unique solvent properties of HMPA have been reviewed.<sup>4a</sup> It has attractive solvation properties, which facilitates the preparation of dianions<sup>4b</sup> and accelerates nucleophilic reactions. Use of HMPA avoids undesired side reactions, since it does not itself metalate or compete for base as do the basic solvents dimethylsulfoxide and  $N,N$ -dimethylformamide.<sup>5,6</sup>

HMPA as a strong basic cosolvent has a yield-lowering effect on alkylation of dianionic  $\alpha$ -branched acids, in contrast to its yield-enhancing effect on alkylation of dianionic  $n$ -aliphatic acids. Yields are only slightly lowered for  $\alpha$ -butylation of isobutyric acid but dramatically lowered (9-15%) in the case of  $\alpha$ -butylation of  $\alpha$ -butyl acids. Reaction of  $n$ -octyl bromide with metalated 2-butyl heptanoic acid in THF-hexane-HMPA allowed isolation of extensive amounts of 1-octene (80-85%). This evidence, along with the trend seen in Table I, indicates that as the extent of chain branching of the acid increases, elimination in THF-hexane-HMPA becomes significant. It is noteworthy that the substitution/elimination ratio shows a much smaller change without the addition of HMPA.<sup>7</sup>

The synthetic possibilities for preparing secondary acids from  $n$ -aliphatic acids in HMPA solutions are exceptional. These compounds are normally difficult to prepare in high yields. Typically, these compounds are obtained by free radical addition of aliphatic acids to olefins in yields approximating 50-70%.<sup>8</sup> The preparations are generally inefficient by requiring high acid to olefin ratios (>10:1) and are difficult to purify.

The synthetic utility of metalated straight-chain aliphatic acids prepared in THF-hexane-HMPA solutions is now being examined with such reagents as  $\text{CO}_2$ ,  $\text{CS}_2$ , alkyl nitrates,  $\text{O}_2$ , and ethyl formate. Detailed studies of these reactions will be shortly forthcoming.

### Experimental Section

**Solvent Purification.**—THF was dried over sodium, distilled, and then redistilled from a ketyl solution (sodium and benzophenone) before use.

HMPA was distilled from sodium hydride at reduced pressure and stored over molecular sieves.

(4) (a) H. Normant, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1046 (1967); (b) H. Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, 1881 (1965); see this reference for other examples of dianions prepared in HMPA.

(5) T. J. Wallace, H. Pobiner, and A. Schriesheim, *J. Org. Chem.*, **30**, 3768 (1965).

(6) Complete lithium-hydrogen exchange between DMSO and the dianion species is noted at 0°.

(7) Amounts of 1-octene isolated from the reaction of 1-bromooctane and metalated 2-butylheptanoic acid in THF-hexane are in the order of 30%.

(8) (a) A. D. Petrov, G. I. Nikishin, and Yu. N. Ogibin, *Dokl. Akad. Nauk SSSR*, **131**, 580 (1960); (b) T. Perlstein, A. Eisner, W. C. Ault, and P. A. DeHaven, *J. Amer. Oil Chem. Soc.*, **45**, 859 (1968).

**Procedure.**—The procedure described here for the preparation of 2-butylheptanoic acid is typical of the method used for all the acids mentioned in Table I.

**2-Butylheptanoic Acid.**—Anhydrous THF (35 ml) and diisopropylamine (4.9 g, 0.049 mol) was added to a dry, nitrogen-flushed flask under an atmosphere of nitrogen. *n*-Butyllithium in hexane (30 ml of 1.6 *M*, 0.048 mol) was added to the magnetically stirred solution at such a rate as to maintain the temperature below 0°. *n*-Heptanoic acid (2.95 g, 0.0227 mol) was then added to the cold basic solution and again the temperature was kept below 0°. After 15 min, HMPA (9 ml, 0.050 mol) was added to the milky white solution, which became transparent and light yellow after 5 min of stirring at 5°. The solution was stirred for an additional 15 min at 5°, and *n*-butyl bromide (3.3 g, 0.024 mol) was added at once at 0°. The reaction temperature immediately rose to 18°. After 2 hr of additional stirring at room temperature, the reaction was worked up in the following manner. Dilute hydrochloric acid (10%) was added at 0° until the mixture became acidic. The aqueous layer was separated and extracted with petroleum ether (bp 30–60°). The combined organic layers were washed five times with 100-ml portions of dilute hydrochloric acid, H<sub>2</sub>O, and saturated sodium chloride solutions. The organic layer was then dried and the solvent was stripped off. The residue was distilled through a 5-in. Vigreux column to give 4.06 g (96%) of a colorless oil, bp 175–177° (30 mm). Examination of this oil on a gas chromatographic column (0.25 in. × 6 ft, 25% DEGA, phosphoric acid treated 60–80 Chromosorb A) at 180° showed this product to be 96.5% 2-butylheptanoic acid and 3.5% *n*-heptanoic acid.

**Registry No.**—HMPA, 680-31-9; 2-butylheptanoic acid, 22058-70-4.